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Reactions of Aromatic Acid Chlorides with Grignard Reagents

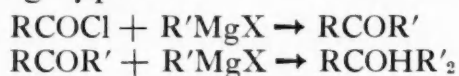
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TISSIER AND GRIGNARD, in 1901, first reported the treatment of an acid chloride with a Grignard reagent. This investigation involved the reaction of acetyl chloride and of benzoyl chloride with an excess of methylmagnesium iodide. In both instances the principal product isolated was the tertiary alcohol, but in the case of the acetyl chloride some acetone was obtained. The study of the behavior of acid halides with Grignard reagents has been greatly expanded since this original work, but until quite recently the field of aromatic acid halides has been somewhat neglected.

The products normally obtained from Grignard treatment of an aroyl halide are the ketone and tertiary alcohol, the ratio varying with the reactant and the attendant conditions. Gilman, Fothergill, and Parker found that treatment of benzoyl chloride with one equivalent of a Grignard reagent gave principally the tertiary alcohol, very little ketone being formed. However, when but 0.6 of a molar equivalent was used, the yield of ketone rose to almost 50%. In a later investigation, Gilman and Mayhue reported that by rapid addition of a molar equivalent of the Grignard reagent to the acid chloride, the ketone was obtained as the principal product. Ent-

mann and Johnson showed that the reactivity of the $-\text{COCH}_3$ group toward a Grignard reagent is greater than that of the $-\text{COCl}$ group, whereas the reactivity of $-\text{COC}_6\text{H}_5$ is almost the same as that of $-\text{COCl}$. Therefore, in a reaction of the following type—



the nature of both R and R' has a great effect upon the products obtained under a given set of conditions.

The reaction of an acid halide with a Grignard reagent is assumed to occur either by direct substitution of an alkyl group for the halogen, or by addition of the Grignard reagent to the carbonyl group followed by the elimination of a molecule of magnesium dihalide. There is at present no definite answer as to which of these possibilities is correct; however, the majority of available evidence favors the mechanism involving addition to the carbonyl group. Entmann and Johnson also showed that the order of reactivity of acid halides with Grignard reagents is $\text{RCOF} > \text{RCOCl} > \text{RCOBr}$, which is the reverse of the usual order for organic halides. This inverse activity indicates that the mechanism is definitely not one of simple metathesis involving only the halogen atom. Fur-

ther evidence of this fact is found in the work of Fuson and his co-workers on 2,4,6-trichloro- and 2,4,6-tribromobenzoyl chloride. When either of these compounds is treated for several hours, at room temperature, with 0.5 molar methylmagnesium bromide, no change occurs; the obvious reason for this inactivity is the steric effect of the ortho halogen atoms. This effect would be of no consequence if the reaction involved only metathesis, but it would greatly hinder addition to the carbonyl group.

Although the normal reaction of an acid halide with a Grignard reagent may involve addition, the possibility is not excluded that variations in the activity of the halogen atom may alter the mechanism or the course of the reaction. Various means of investigation show definitely that the reactivity of the halogen atom attached to the carbonyl group in aroyl halides varies greatly when the benzene nucleus is substituted, and also with the position of the ring substituent. Many methods have been used in this investigation, but the most satisfactory results have been obtained by hydrolysis or alcoholysis.

In general, a substituent in the ortho position in benzoyl chloride appears to increase the activity of the halogen. Negative groups in the meta or para positions apparently enhance the activity of the halogen, but a methyl group alone, in either of these two positions, produces the opposite effect. A typical

example of the variation in velocity constants for hydrolysis of substituted benzoyl chlorides is found in the bromo derivatives. The values are as follows—

Compound	K
$\text{C}_6\text{H}_5\text{COCl}$	0.026
$\text{o-BrC}_6\text{H}_4\text{COCl}$	0.035
$\text{m-BrC}_6\text{H}_4\text{COCl}$	0.044
$\text{p-BrC}_6\text{H}_4\text{COCl}$	0.024
$\text{2,6-Br}_2\text{C}_6\text{H}_3\text{COCl}$	0.00029
$\text{2,4-Br}_2\text{C}_6\text{H}_3\text{COCl}$	0.057
$\text{3,5-Br}_2\text{C}_6\text{H}_3\text{COCl}$	0.35

It can be seen from the table that 2,6-dibromobenzoyl chloride is a notable exception to the hypothesis that ortho substituents increase the halogen activity. A comparable decrease in activity has been reported with 2,4,6-tribromobenzoyl chloride. This decreased activity is apparently a result of the steric effect of the two ortho halogens, and is evidence that the hydrolysis of an acid chloride is also an additive mechanism.

In the case of 2,4,6-trimethylbenzoyl chloride, the methyl groups are apparently not large enough to offer significant hindrance to hydrolysis, for this compound is more reactive than benzoyl chloride. The increased activity of 2,4,6-trimethylbenzoyl chloride and of its triethyl homolog gives rise to a variation from the normal course when either of these compounds is treated with a Grignard reagent. When the acid chloride is slowly added to one mole of the Grignard reagent, the expected ketone is formed. On the other hand, when the

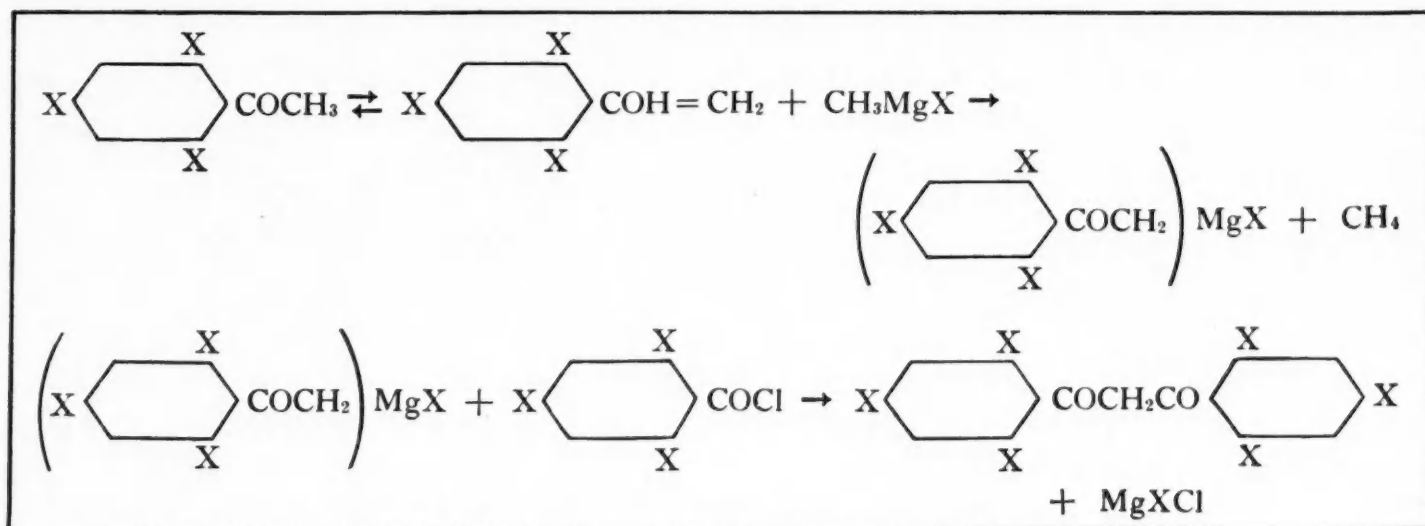


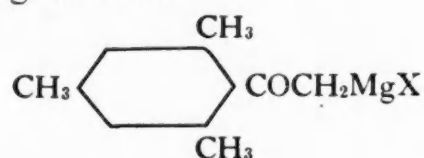
FIGURE 1—Reactions involved in the preparation of a dibenzoyl methane.

Grignard reagent is added to one mole of the acid chloride, the product is an equimolar mixture of the ketone and a benzil that is formed by direct coupling of the acid chloride. This coupling is similar to that obtained when certain metallic halides are treated with a Grignard reagent.

Probably the most interesting reaction directly caused by substitution in the aromatic nucleus is the formation of a dibenzoyl methane from 2,4,6-trichloro- or 2,4,6-tribromobenzoyl chloride and a methylmagnesium halide. Apparently a ketone is the first product, which then reacts further as indicated in Figure 1. The reaction (not illustrated) of the acid chloride with the Grignard reagent is apparently so slow that the subsequent reaction can compete very readily. This mechanism has been established definitely by converting the 2,4,6-trihalogenated acetophenone to the magnesium halide derivative and then adding the corresponding acid chloride; the result is a very high yield of the substituted dibenzoyl methane. The 2,4,6-trihalogenated acetophenone may be prepared from the trihalogenated benzoyl chloride

by slowly adding the acid chloride to a 5-6 molar Grignard solution in benzene and keeping the temperature at 100° C.

In 1902, it was discovered that acetomesitylene would form a Grignard derivative that would regenerate the parent compound when added to water. It was only recently, however, that Kohler and his co-workers showed the true nature of this derivative. The conditions that led to the formation of dibenzoyl methanes, as described in the preceding paragraph, caused Fuson, Fugate, and Fisher to carry the study of this acetomesitylene derivative even further. They demonstrated that this compound behaves in many ways like a normal Grignard reagent having the following structure—



It reacts with acid chlorides to give the expected 1,3-diketone, and the same product is obtained with esters. Ketones and aldehydes give the normal carbinols. In addition, some coupling of the reagent is obtained with cupric chloride.

Eastman Organic Chemicals as Analytical Reagents

REAGENTS FOR IRON

QUERCETIN

Kocsis: *Mikrochemie*, **25**, 13-15 (1938)

Quercetin can be used as a spot test reagent to detect as little as 3 γ of iron or uranium. In the presence of a 0.2% solution of the reagent, ferrous or ferric iron develops an olive-green color and uranium a rust-brown color.

α, α' -DIPYRIDYL

Schulek and Floderer: *Chem. Absts.*, **33**, 4901 (1939)

Either ferrous or ferric iron, or both, can be determined colorimetrically by the use of α, α' -dipyridyl. If the total iron content is to be determined, the trivalent form is reduced with sulfurous

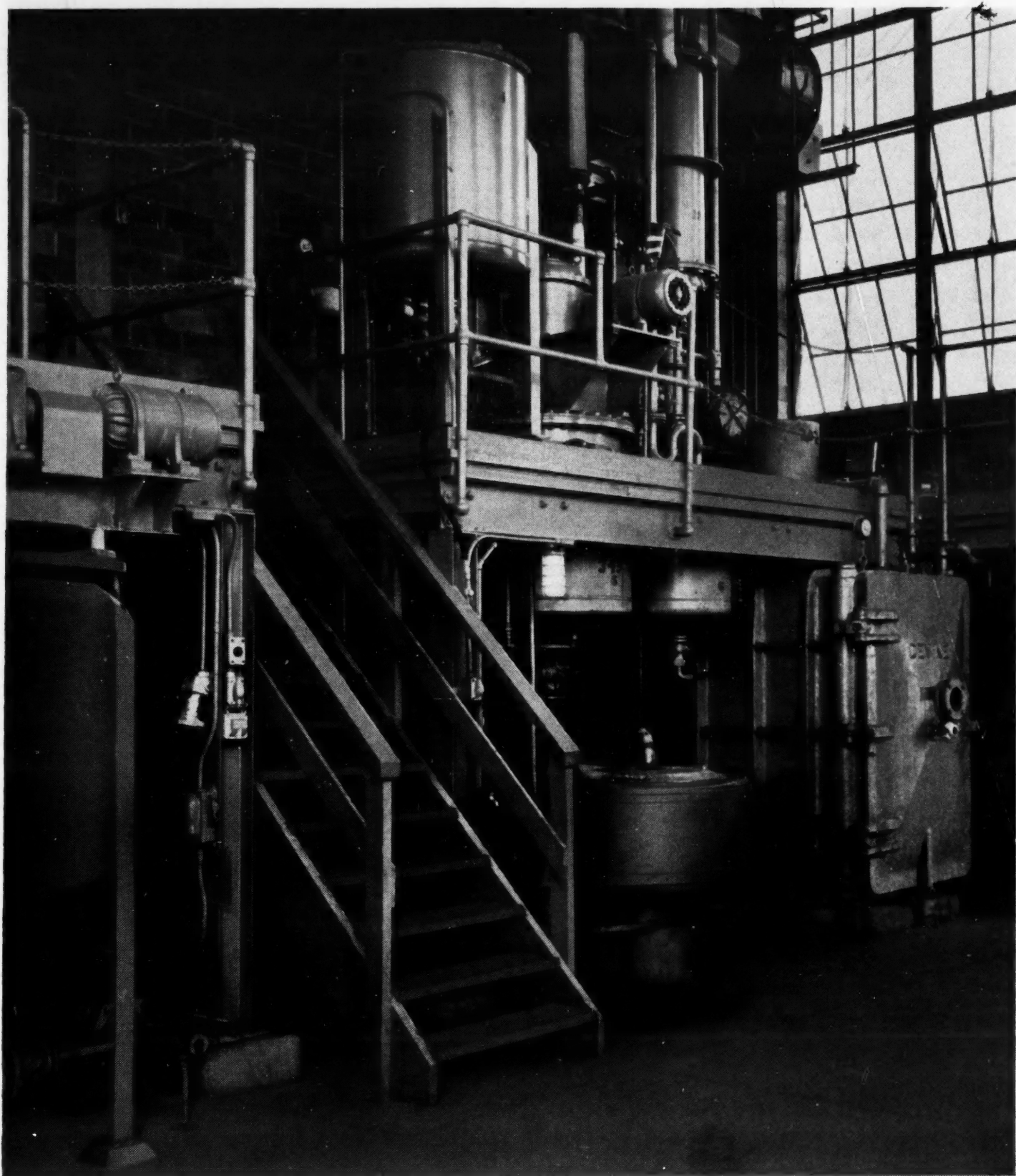
acid; sulfuric acid, phosphoric acid, and a 1% solution of dipyridyl are added, and the mixture diluted to 100 cc. The extinction coefficient of this solution is determined and compared with a blank.

Ferrous and ferric iron may be determined separately by first determining the ferrous iron, and then reducing the trivalent form and analyzing the solution for its total iron content.

Special Notice

In the future, SYNTHETIC ORGANIC CHEMICALS will carry a different volume designation each calendar year, irrespective of the number of issues. In line with this change, there were only four issues in Volume 12.

Organic Chemicals in Commercial Quantities



MOST CHEMISTS think of Eastman Organic Chemicals as pure compounds that are available only for research and experimental purposes. Yet a number of these chemicals are prepared in commercial and semicommercial quantities for industrial uses.

The apparatus shown above is part of that employed in the large-scale produc-

tion of these compounds. Glass-lined equipment is used wherever possible, to prevent contamination. This safeguard, together with constant control during preparation, assures the commercial consumer that he will receive chemicals of research quality. As a further advantage, industrial quantities of these compounds are moderately priced.